

New paradigms for *BRCA1/BRCA2* testing in women with ovarian cancer – results of the Genetic Testing in Epithelial Ovarian Cancer (GTEOC) Study

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Abstract

Background: Over recent years genetic testing for germline mutations in *BRCA1/BRCA2* has become more readily available because of technological advances and reducing costs. The Genetic Testing in Epithelial Ovarian Cancer (GTEOC) Study explored the feasibility and acceptability of offering genetic testing to all women recently diagnosed with epithelial ovarian cancer (EOC).

Methods: From 1st July 2013 to 30th June 2015 women newly diagnosed with EOC were recruited through six sites in East Anglia, UK. Eligibility was irrespective of patient age and family history of cancer. The psychosocial arm of the study utilised self-report, psychometrically validated questionnaires (Depression Anxiety and Stress Scale, DASS-21; Impact of Event Scale, IES) and cost analysis was performed.

Results: 232 women were recruited and 18 mutations were detected (12 in *BRCA1*, 6 in *BRCA2*) giving a mutation yield of 8% which increases to 12% in unselected women <70 years (17/146) and 1% in unselected women \geq 70 years (1/86). IES and DASS-21 scores in response to genetic testing were significantly lower than equivalent scores in response to cancer diagnosis ($p<.001$). Correlation tests indicated that whilst older age is a protective factor against any traumatic impacts of genetic testing, no significant correlation exists between age and distress outcomes.

Conclusion: The mutation yield in unselected women diagnosed with EOC from a heterogeneous population with no founder mutations was 8% in all ages and 12% in women under 70. Unselected genetic testing in women with EOC was acceptable to patients and is potentially less resource-intensive than current standard practice.

Introduction

Approximately 1.5% of women will be diagnosed with epithelial ovarian cancer (EOC) in their lifetime and, as a result of the relatively poor prognosis, it is the fifth commonest cause of cancer-related mortality in females. In the mid 1990s germline mutations in the *BRCA1* and *BRCA2* genes were identified in families with hereditary breast and ovarian cancer and testing for these genes is available through the NHS genetic service providing that the family history is sufficiently strong to instigate a referral (NICE guideline CG41). A woman with a mutation in the *BRCA1* gene has a 40-60% lifetime risk of developing EOC[1]. For *BRCA2* the lifetime risk is lower at 10–30%, but this is still around 10-fold elevated compared to the general population risk. At present there is no proven clinical screening for EOC [2] and unaffected women with completed families who carry *BRCA1/BRCA2* mutations typically elect to have a prophylactic bilateral salpingo-oophorectomy that reduces the risk of EOC by 80–96% [3-5]. The prevalence of *BRCA1/BRCA2* mutations in unselected women with ovarian cancers ranges from 8 to 22%[6-10], and this variation can in part be explained by the presence or absence of founder mutations in the study populations. In one study of 1,342 unselected patients with invasive ovarian cancer 161 *BRCA1/BRCA2* carriers were identified in 1,038 women diagnosed with high-grade serous (HGSOC) or endometrioid (EC) ovarian cancer (overall frequency 15.5%) confirming that inherited mutations in these genes account for a significant minority of all ovarian cancer cases [9]. The frequency of mutations was highest in the HGSOC group (135 carriers, 18%) but also significant in women with EC (26 carriers, 9%). Family history of breast or ovarian cancer was the best predictor of carrier status (33% had a first degree relative with breast or ovarian cancer) but 7.9% of all carriers had no significant family history.

Genetic testing for mutations in *BRCA1/BRCA2* was introduced into clinical practice in the late 1990s but because of the cost and technical complexity of testing it was initially limited to those cases where there was a greater than 20% probability of detecting a mutation (NICE guideline CG41), with the threshold being lowered to 10% since 2013 (NICE guideline CG164). Various models, such as BOADICEA [11] and the Manchester score [12], have been developed to estimate the probability of finding a *BRCA1/BRCA2* mutation. While these are extensively used in Clinical Genetics centres, they have in general not been incorporated into routine clinical practice outside of Clinical Genetics. Despite increasing awareness of *BRCA1/BRCA2* in the medical community, referral rates vary considerably and many women are not referred for a genetic assessment; only 20% of the cohort studied by Zhang *et al.* had previously been referred for genetic testing [13] and as the referred group only contained 60% of all mutation carriers, it meant that 40% of mutation carriers were missed. If more mutation carriers can be identified this will increase the numbers of families where cascade genetic testing can be offered so that more female relatives at high risk of EOC and breast cancer can be identified, counselled and managed appropriately.

BRCA1/BRCA2 mutation carriers with EOC have a better short term survival compared with non-*BRCA1/BRCA2* women [14] and there is emerging evidence that *BRCA2* mutation status in particular is likely to be an important prognostic and predictive marker in EOC with a significantly higher primary chemotherapy sensitivity rate [14 15] although the survival difference becomes less apparent over time [16]. It also appears that *BRCA1/BRCA2* mutation status provides predictive information regarding likelihood of response to PARP inhibitors [17 18].

In this study we explored the acceptability and feasibility of universal testing without pre-test genetic counselling *BRCA1/BRCA2* in an unselected population of women who were within 12 months of being diagnosed with EOC. We used established metrics (the Depression Anxiety and Stress Scale, DASS-21 and the Impact of Event Scale, IES) to assess psychological distress, tailored questionnaires to gauge acceptability and undertook a detailed cost analysis to compare resource use with the standard genetic testing model.

Methods

Patient eligibility Patients were eligible if they were over 18 years old and had been diagnosed with high-grade serous or endometrioid epithelial ovarian cancer within the last 12 months. Other ovarian cancer subtypes including low grade tumours were excluded as they are not part of the *BRCA1/BRCA2* phenotype [9]. The study had full ethical approval (REC12/EE/0433).

Patient recruitment: Women were recruited through six NHS hospitals of different sizes ranging from smaller district general hospitals to large regional centres (Figure 1). All women with ovarian cancer in the East Anglia region are managed in these six institutions, which allows for near-complete ascertainment of cases. Eligible women were approached by their treating clinician or specialist nurse. If the patient expressed interest in the study, information about the patient was passed to the study coordinator who provided the patient with detailed information about the study and obtained informed consent. Additionally the letter was sent to the patient to collect her demographic details and family history (Figure 2). No formal genetic counselling was given prior to testing.

Genetic counselling and testing process: *BRCA1/BRCA2* testing was performed in the clinically accredited laboratory of the East Anglian Genetics Service by Next Generation Sequencing and MLPA. If a gene mutation was identified the patient, her general practitioner and her treating clinician were informed by letter from the study team and a referral to the NHS clinical genetics service was requested for genetic counselling and cascade testing of other at-risk family members. Where variants of unknown significance (VUS) were identified these were also fed back to the participant, GP and her clinician by letter, and again a referral for genetic counselling was requested (Figure 2). Only those women with mutations or VUS

received formal post-test genetic counselling via the standard clinical service. All family histories were assessed by a Geneticist when the mutation report was generated. If there was a clinically relevant family history that met standard referral criteria in women with no mutations this was noted in the results letter to the participant with advice to seek a genetics referral.

Cost-analysis: In order to determine the resource implications of offering universal *BRCA1/BRCA2* testing in an unselected population of women within 12 months of being diagnosed with EOC we undertook a cost-analysis. We mapped both the existing (current standard) referral and testing pathway (Figure S1) and the new proposed referral and testing pathway (Figure S2). Once these pathways were mapped, we defined the service activities and determined the resources required to undertake these activities using a 'bottom-up' micro-costing approach in order to calculate the overall cost for both pathways. Costs are reported in 2015 UK £ and from the perspective of the clinical genetics service from referral for genetic testing to diagnostic *BRCA1/BRCA2* test outcome of the index case. Market prices taken from the NHS test directory hosted on the UKGTN website (<http://ukgt.nhs.uk>) were used for the actual genetic testing of *BRCA1/BRCA2*. The cost of staff (administrators and clinical staff) were obtained from both the NHS agenda for change (2015) and the Personal Social Services Research Unit (PSSRU) reference costs for 2014/2015. We used the mid-point of each grade and included National Insurance, superannuation and overhead costs if they were not already included. All cost data collected are reported in Table S1. Here we report the average testing pathway cost per *BRCA1/BRCA2* mutation identified, the average testing pathway cost per genetic test offered, and the overall budget required for the 232 EOC patients eligible for inclusion within the GTEOC study.

The main (base case) analysis assumes that in addition to those meeting the Manchester score for genetic testing (n=63 of the 232 EOC patients), half (50%) of those affected by epithelial ovarian cancer were also referred through to the cancer genetics service to have their family history checked before determining whether they would have genetic testing. The base case analysis does not have an age cut-off and no discount rate has been applied given that all patients would expect to receive the result of their genetic test within a year.

Cost-analysis sensitivity analysis: Sensitivity analyses allow insight into which assumptions or limitations to the data included are important to the overall result or conclusion drawn from the analysis. A pragmatic approach to conducting one-way sensitivity analyses was undertaken and included varying the cost of the genetic test (assay price in both pathways), percentage of patients referred to the cancer genetics service in the existing current testing pathway (from 0% of patients not meeting the Manchester score to 100% i.e. all

patients offered initial appointment in cancer genetics service), and limiting the genetic testing within the GTEOC testing pathway to women under 70.

Psychological impact and acceptability analysis: All participants who underwent genetic testing were asked to complete a short, self-report questionnaire which was sent to them by post to limit intrusion. This included the Depression, Anxiety and Stress Scale (DASS-21)[19] and the Impact of Event Scale (IES)[20]. Each scale was presented twice: once anchored to the psychological impact of diagnosis of ovarian cancer, and a second time anchored to the psychological impact of the genetic test. A further twelve study-specific questions assessed the acceptability of this method of genetic testing.

Results

A total of 232 of 281 eligible women (83%) were consented to participate and tested over the study period. Almost all (98%) participants reported their ethnicity as white British, in keeping with the demographic profile of the region (Table 1). The mean age of the participants was 63 years (range 30-90 years) and two-thirds of the participants were 60 years or older which is consistent with the observed age profile in women diagnosed with EOC. One hundred and ninety one participants (82%) had high-grade serous ovarian cancer, 20 (9%) had endometrioid OC, 15 (6%) had unspecified or poorly differentiated adenocarcinomas and six (2.5%) were mixed types. The median time from consent to results delivered was 46 working days (range 15-117 days). The mean time from sample receipt to results delivered was 39 working days (range 11-111 days). Overall, 175 women (75%) had stage III or IV disease. Educational levels were available on 166 participants (72%) and in this group of women 100 (60%) had completed secondary education only, 37 (22%) had completed a diploma and 25 (15%) were educated to degree level (Table 1).

Eighteen *BRCA1/BRCA2* predicted loss-of-function mutations were detected (12 in *BRCA1*, six in *BRCA2*) giving an overall prevalence of 8% (Table 2). None of the mutations were common founder mutations seen in other populations (Table S2)[21]. The mean age of mutation carriers was 50 years (range 40-75 years) with a mutation prevalence of 12% in women under 70 years of age (17/146) and 1% in unselected women 70 or older (1/86).

In women under 70 years of age with a positive family history (affected first- or second-degree relative) the mutation prevalence 17% (13/77), but one quarter of the carriers in this age group had no family history. Six mutation carriers had a previous personal history of breast cancer (Table 2). All twelve *BRCA1* and five of the *BRCA2* mutation positive cases had high-grade serous ovarian cancer (Table 2). The other *BRCA2* mutation positive case had a high-grade adenocarcinoma with features suggestive of an endometrioid adenocarcinoma. Seventeen VUS were detected in 15 patients, 14 in *BRCA1* and 3 in *BRCA2*.

All 12 *BRCA1* and five of the *BRCA2* mutation positive cases had serous papillary type ovarian cancer (Table 2). One of the *BRCA2* mutation positive cases had high grade adenocarcinoma with features in favour of a grade 3 endometrioid adenocarcinoma.

Psychological impact: 173 questionnaires were returned (75%). IES (cognitive intrusion i.e. unwanted intrusive thoughts about the phenomenon, avoidance behaviour, hyperarousal i.e. a state of increased psychological and physiological tension) and DASS-21 (depression, anxiety and stress) scores in response to genetic testing were significantly lower than equivalent scores in response to cancer diagnosis (Wilcoxon Signed Rank tests Z-score range = -6.174 to -8.852; all $p < .001$). Essentially, having the genetic test did not increase distress or psychological traumatic response beyond that already being experienced as a result of the cancer diagnosis itself. Younger participants found the test to lead to more intrusive thoughts (IES intrusion $r = -.172$, $p = .026$), and significantly more stress (DASS stress $r = .162$, $p = .014$). There were no significant differences based on age for IES avoidance IES hyperarousal, DASS anxiety or DASS depression. There were no significant differences on any IES or DASS subscale by education level, cancer stage, Manchester Score or previous cancer history. A significant difference was found in cognitive avoidance scores based on categorisation of *BRCA* mutation status ($p = .036$), with highest mean scores reported by those with a *BRCA1* or *BRCA2* mutation. The study population was not sufficiently heterogeneous to explore any differences based on either ethnicity or country of birth.

Acceptability of the test: High levels of acceptability were reported (Table 3) and participants felt they had enough information and time to proceed with genetic testing. Most women talked to their family about the test and felt that the test gave them a better understanding of their family's risk. The widest variation in scores related to the perceived level of ease with which participants made the decision to proceed with genetic testing.

Cost analysis: For the base case analysis, the overall budget, the average patient pathway cost per *BRCA1/BRCA2* mutation positive, and the average patient pathway cost per test offered for the current pathway were £142,702, £11,892, and £2,265, respectively. For the GTEOC patient pathway, these costs were £253,617, £14,919 and £1,093, respectively (Table S2). The larger budget for the GTEOC patient pathway represents the increased cost due to a significantly greater number of genetic tests undertaken. When the cost of the genetic testing is removed from the cost of the patient pathway, the budget for GTEOC patient pathway is lower (£56,166 versus £88,633 for the current patient pathway). The non-genetic test related costs within the GTEOC patient pathway account for approximately 22% of the budget compared to 62% for the current patient pathway within the base-case analysis. The average patient pathway cost per patient without the genetic testing for the GTEOC and the current testing patient pathway are £243 and £383, respectively.

Sensitivity analysis: The results of the sensitivity analysis show that changing the cost of the genetic test has a large impact on the budget, the average patient pathway cost per *BRCA1/BRCA2* positive and also the average testing pathway cost per test offered for both pathways (Table S2). If the cost of the genetic test were to come down to £190, the budget required for the GTEOC pathway would be the same as the current pathway *ceteris paribus* in the base case analysis. Changing the number of women referred to the cancer genetics service impacts on the budget required for the existing pathway. Implementing the age cut-off for eligibility of genetic testing in the GTEOC pathway has a large impact on the budget required to test the 232 eligible women. Even with a genetic test price of £650 (the current price of a clinical exome), implementing the age cut-off within the GTEOC patient pathway would lead to a lower budget for the GTEOC pathway (£121,229 versus £130,102 for the current patient pathway).

Conclusions

The primary objective of the study was to determine the feasibility, acceptability and cost-effectiveness of Is screening all newly diagnosed women with EOC for *BRCA1/BRCA2* mutations by determining the mutation prevalence, calculating cost per gene mutation detected and assessing psychological impact based on questionnaire responses and qualitative interviews.

The mutation prevalence in an unselected cohort of women diagnosed with EOC from a heterogeneous population with no founder mutations was 8% in all ages and 12% in women under 70 years. This is similar to that reported in a combined study of two large case-control OC series (one of which included cases from the East Anglia region)[8], but lower than that the frequency of 15% reported a recent study by Norquist *et al.* [10]. These differences are likely to be partly explained by the presence or absence of founder mutations in the test populations as 13% of all the *BRCA1/BRCA2* mutations identified in the Norquist study were those commonly found in individuals of Ashkenazi Jewish descent.

The cost-analysis undertaken here provides some insight into the potential delivery of *BRCA1/2* genetic testing in a cohort of women diagnosed with EOC. The burden of cost in the provision of genetic testing lies in the provision of diagnostic testing for the current patient pathway (62% of costs are non-genetic test related) whereas with the GTEOC pathway the burden lies with the cost of the genetic testing itself (only 22% of costs were non-genetic test related). Furthermore, given the high price of genetic testing used within the base-case, when a more realistic current day price is included as a sensitivity analysis and is coupled with the use of an age cut-off, the GTEOC patient testing pathway is likely cost-saving compared to the current testing pathway for this patient cohort. However, a clear limitation of this analysis is the exclusion of the costs involved in the clinical management of these patients as these costs are likely to be significant when cascade testing is also included into the 'patient' pathway.

Based on our findings we would recommend offering testing to all women under 70 years of age as the mutation prevalence would be above the current threshold of 10% used for eligibility for testing breast cancer families in the UK (NICE CG164). This age cut-off would also improve the mutation: VUS ratio from 1:1 to 2:1. By not testing those over 70 years it is possible to reduce the number of tests by around 37% and miss only 6% of all mutations. Indeed, in this study both women over the age of 70 years with mutations had a family history of breast or ovarian cancer. No mutation carriers would have been missed by using the criteria of 1) age under 70 years, or 2) 70 years and over with a previous history of breast cancer or history of breast or ovarian cancer in a first degree relative.

A key question of the GTEOC study was whether outcome of the genetic test affects IES or DASS-21 scores. Our study investigated the hypothesis that psychological response to the genetic test may lead to increased distress beyond that of the cancer diagnosis itself. Methodologically, this was difficult to test and we used the approach of including each psychological measure twice (with different anchoring) to let participants distinguish their psychological responses to the genetic test from their psychological response to the cancer diagnosis itself. That participants responded differently to identical questions anchored to each event suggests that this is a useful methodology; mean ratings on all subscales of both the IES and the DASS were significantly higher for diagnosis than for the genetic test, consistent with previous findings in breast cancer patients [22]. We also investigated whether the psychological response to the genetic test would be affected by participant demographics. Correlation analyses indicated no significant effects of age on depression, anxiety cognitive avoidance or hyperarousal; significant negative correlations indicate an inverse relationship between younger age and higher levels of perceived stress and cognitive intrusion. This result fits the pattern of broader literature on the psychological impact of cancer diagnosis and treatment, whereby adjustment is typically worse in those diagnosed at a younger age [23]. Those later found to have a genetic mutation scored significantly higher on cognitive avoidance, but no differences in other subscales assessed were identified. Self-reported acceptability data were favourable and support the value and acceptability of the testing procedure in this sample.

Genetic counselling protocols have evolved from a paradigm initially developed in the context of predictive testing for Huntington's disease (HD). Due to concerns about the negative and potentially grave impact of receiving a molecular diagnosis of HD, a protocol involving two face-to-face pre-test appointments and follow up was developed [24]. It has long been thought that this level of support may not be required in the diagnostic setting[25] and with the advent of targeted therapies the need for systematic genetic testing has become more pressing, but current pathways are not designed for high volume testing. One solution would be to devolve genetic testing completely to the oncologists but this approach fails to take advantage of the comprehensive clinical genetic networks that exist in most countries. There are also other concerns

regarding this approach; the interpretation of VUS may not be adequate[26], and cascade testing within families may not occur (Figure 3).

A unique strength of this study is the near complete ascertainment of women with ovarian cancer recruited through both secondary and tertiary referral centres in a clearly defined geographical region which is highly representative of clinical services throughout the UK and internationally. These findings are therefore likely to be widely applicable, and similar novel approaches have been trialled in other countries such as Norway [7] and The Netherlands [27]. Even though overall numbers tested are relatively small, the participation rate was high and the mutation yield is consistent with those reported in other studies in heterogeneous populations lacking founder mutations. One weakness is the lack of ethnic diversity in the study participants which reflects the relative homogeneity of the East Anglian population (91% white Caucasian for all ages; *Office for National Statistics, 2011 Census data from KS201EW*). Further studies would be required to assess acceptability in more ethnically diverse regions.

These results show universal genetic testing in women with a diagnosis of EOC to be an acceptable and sensitive procedure: these women have much emotional work to do as they confront their diagnosis, mortality and the impact on family members. Our data show that this type of genetic testing does not increase distress or traumatic response significantly beyond that already experienced following cancer diagnosis. Older age was a protective factor against traumatic response, but not distress. Comprehensive case-based genetic testing appears to be acceptable to patients and is less resource-intensive than standard current practice where all women are referred for genetic counselling prior to testing.

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Contributors

MT, JB, PP and RC conceived the idea, developed the study protocol and oversaw the project. IP and HS coordinated the running of the study, JD, ET and StAb coordinated the mutation analysis, HS and NHW performed the psychosocial analysis, VB and SG performed the health economic analysis, MJ-L performed the pathological review. BN, CH, EB, PR, RN, SM, AD, VL, HW, LTT, MD, SaAy, BR, HE, CP, TD assisted with the recruitment of study participants. MT drafted the manuscript and all authors read and approved the final version.

Competing Interests

The authors have no competing interested to declare

Patient Consent Obtained

Ethical Approval (REC12/EE/0433).

Data sharing Patient level data and the full dataset is available from from the corresponding author. Participants gave informed consent for data sharing.

Tables

| Demographic | | n |
|-------------------------------------|----------------|--------------|
| Mean Age, years (range) | | 64.3 (30-90) |
| Country of Birth | UK | 224 (97%) |
| | Other | 8 (3%) |
| Ethnicity | Caucasian | 226 (98%) |
| | Other | 6 (2%) |
| Pathology | Serous | 192 |
| | Endometrioid | 20 |
| | Adenocarcinoma | 15 |
| | Mixed | 5 |
| Stage | I | 34 |
| | II | 6 |
| | III | 137 |
| | IV | 42 |
| | Not classified | 13 |
| Educational Status (total n=166) | Degree | 25 (15%) |
| | Diploma | 37 (22%) |
| | Secondary | 100 (60%) |

Table 1 Study population demographics

| | <i>BRCA1/2+</i> (n= 18) | <i>BRCA1/2</i> VUS (n=15) | Non- <i>BRCA1/2</i> (n= 199) |
|-------------------|--------------------------|----------------------------|------------------------------|
| Mean Age (Range) | 49.5 (40-75) | 64.8 (41-84) | 66.1 (30-90) |
| <i>BRCA1</i> | 12 (67%) | 3 (20%) | N/A |
| <i>BRCA2</i> | 6 (33%) | 12 (80%) | N/A |
| Pathology: | | | |
| High grade serous | 15 | 11 | 166 |
| Endometrioid | 1 | 4 | 15 |
| Adenocarcinoma | 2 | 0 | 13 |
| Mixed types | 0 | 0 | 5 |
| Stage: | | | |
| I | 4 | 5 | 25 |
| II | 0 | 0 | 6 |
| III | 12 | 9 | 116 |
| IV | 2 | 1 | 39 |
| Not classified | 0 | 0 | 13 |

Table 2 – Age at diagnosis and pathology characteristics of *BRCA1/BRCA2* mutation carriers

| Question | n | Mean Score | SD |
|--|-----|------------|------|
| Q1: I was pleased to have the option of genetic testing <i>High mean score = pleased to have option of genetic test</i> | 173 | 5.72 | .846 |
| Q2: I had access to enough information to make a decision about testing <i>High mean score = had enough information to make decision</i> | 174 | 5.61 | .953 |
| Q3: It was difficult to decide whether to have the genetic test <i>Low mean score = easy to make decision</i> | 172 | 2.05 | 1.80 |
| Q4: I had enough time to think about whether to have the genetic test <i>High mean score = had enough time to make decision</i> | 174 | 5.43 | 1.29 |
| Q5: I found genetic testing to be useful to me <i>High mean score = genetic test was useful</i> | 172 | 5.49 | 1.07 |
| Q6: I was reassured by my genetic test results <i>High mean score = reassured by test results</i> | 173 | 5.30 | 1.30 |
| Q7: The genetic test results allowed me to better understand my cancer risks <i>High mean score = test allowed better understanding of cancer risks</i> | 173 | 5.00 | 1.48 |
| Q8: The genetic test results allowed me to better understand my family's cancer risks <i>High mean score = test allowed better understanding of family's risk</i> | 173 | 5.31 | 1.26 |
| Q9: This was a good time for me to have the genetic test <i>High mean score = good time to have test</i> | 171 | 5.43 | 1.19 |
| Q10: I would have preferred to wait before I had genetic testing <i>Low mean score = wouldn't have wanted to wait before test</i> | 171 | 1.49 | 1.21 |
| Q11: I found genetic testing to be stressful <i>Low mean score = didn't find it stressful</i> | 170 | 1.75 | 1.53 |
| Q12: I was satisfied with the support I received from family and friends <i>High mean score = satisfied with family / friend support</i> | 168 | 5.52 | 1.13 |
| Q13: I talked to my family about my genetic test <i>High mean score = most talked to their family about the test</i> | 169 | 5.73 | 1.15 |

Table 3 – Quantitative analysis of acceptability using 13 tailored questions

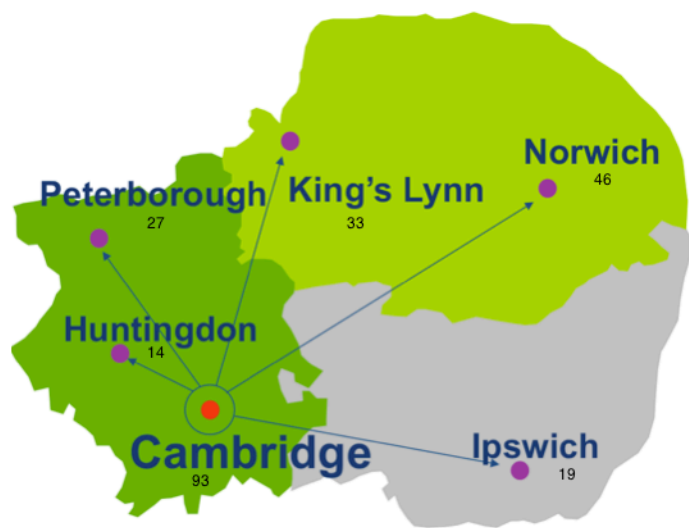
Possible Score range was 1.0 (min) to 6.0 (max)

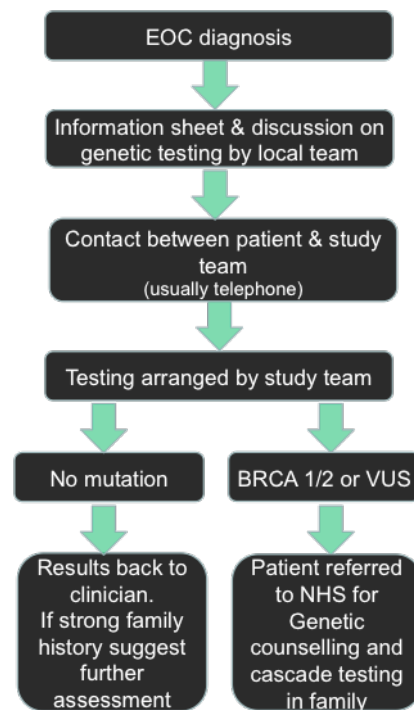
Figure Legends

Figure 1. The location of hospitals in the Anglia region and number of patients recruited at each site.

Figure 2. The GTEOC Testing Protocol

Figure 3. Models of Service delivery for Genetic Testing





Genetics-led

Labour intensive
Time Consuming, Slow
Critically dependent on
Counselling Resources
Tried and Tested
Nationally established
Will miss some mutations

Oncology-led

Streamlined
Universal
Fast
Can it work in a DGH?
Will miss some families



GTEOC

Genetics-coordinated

Streamlined
Close working between
Genetics and Oncology
Universal
Fast

New paradigms for *BRCA1/BRCA2* testing in women with ovarian cancer – results of the Genetic Testing in Epithelial Ovarian Cancer (GTEOC) Study

Supplementary Files

| Resource - activity | Unit cost (£) | Unit description | Source of data |
|--|---------------|---|---|
| Existing pathway | | | |
| Basic family history check in Oncology | 19.28 | This activity involves discussing family history with the patient in order to determine whether the patient is potentially eligible for genetic testing and therefore referral to the cancer genetics service | Primary data collection at CUH NHS Foundation Trust |
| Referred to cancer genetic service (+ve FH) | 65.03 | Patient is sent a letter with FH form to return to cancer genetics service. FH form is received and checked and includes letter sent for appointment or for ineligibility regarding testing | Primary data collection at CUH NHS Foundation Trust |
| Eligible for test, offered appointment and attends cancer genetics service | 434.47 | Patient attends 45 minute appointment with genetic counsellor (70% led) and clinical geneticist (30% led) to provide counselling and offer genetic test | NHS reference costs: financial year 2014-2015 |
| Offered and accepts <i>BRCA1/BRCA2</i> genetic test | 850.00 | NHS test price at Addenbrooke's Hospital. Test involves sequencing of the entire coding region of genes plus copy number analysis. | UKGTN website |
| <i>BRCA1/BRCA2</i> negative | 81.36 | Patient receives result as agreed during appointment either by letter (45%), phone call (45%) or face-to-face appointment (10%) | Primary data collection at CUH NHS Foundation Trust |
| <i>BRCA1/BRCA2</i> VUS | 81.36 | Patient receives result as agreed during appointment either by letter (45%), phone call (45%) or face-to-face appointment (10%) – same as <i>BRCA1/BRCA2</i> negative | Primary data collection at CUH NHS Foundation Trust |
| <i>BRCA1/BRCA2</i> positive | 95.09 | Patient receives result as agreed during appointment either by letter or phone call (85%) or by face-to-face appointment (15%) | Primary data collection at CUH NHS Foundation Trust |
| New proposed pathway | | | |
| Referred to cancer genetic service | 47.28 | Patient details collected by genetic counsellor and processes eligibility for genetic testing over the phone via family history | Primary data collection at CUH NHS Foundation Trust |
| Eligible for test, offered appointment and attends cancer genetics service | 144.82 | Patient attends 15 minute appointment with genetic counsellor (70% led) and clinical geneticist (30% led) to provide counselling and offer genetic | NHS reference costs: financial year 2014-2015 |

| | | | |
|---|--------|--|---|
| | | test | |
| Offered and accepts <i>BRCA1/BRCA2</i> genetic test | 850.00 | NHS test price at Addenbrooke's Hospital. Test involves sequencing of the entire coding region of genes plus copy number analysis. | UKGTN website |
| <i>BRCA1/BRCA2</i> negative | 57.68 | Patient receives result by letter | Primary data collection at CUH NHS Foundation Trust |
| <i>BRCA1/BRCA2</i> VUS | 23.19 | Patient receives result by letter with 20% of patients also receiving a phone call from genetic counsellor | Primary data collection at CUH NHS Foundation Trust |
| <i>BRCA1/BRCA2</i> positive | 385.82 | Patient received result by letter and an appointment is made for patients to attend and discuss results with clinical geneticist | Primary data collection at CUH NHS Foundation Trust |

Table S1: Estimated resources, test unit costs and assumptions (2015)

| Mutations | | | | | | | | | |
|-----------|-------|--|----------------|-----|------------------|-------|-------|----|----------|
| ID | Gene | DNA level | Protein level | Age | Cancer Pathology | Grade | Stage | MS | BOADICEA |
| 100 | BRCA1 | c.325_3255dupGA | Leu1086fs | 54 | SP | 3 | 4 | 13 | 3.2 |
| 126 | BRCA1 | c.2475delC | Asp825fs | 75 | SP | 3 | 3c | 14 | 1.4 |
| 63 | BRCA1 | c.4868C>G | Ala1623Gly | 67 | SP | 3 | 3c | 20 | 4.5 |
| 185 | BRCA1 | c.3307_3308insC | Cys1103Serfs*2 | 40 | SP | 3 | 3c | 25 | 46.1 |
| 8 | BRCA2 | c.4154C>G | Ser1385Ter | 65 | SP | 3 | 3 | 24 | 41.6 |
| 218 | BRCA1 | c.3193dupG | Asp1065fs | 55 | SP | 3 | 3c | 25 | 70.4 |
| 134 | BRCA1 | c.1961delA | Lys654fs | 52 | SP | 3 | 3c | 23 | 27.3 |
| 17 | BRCA2 | c.517-2A>G | | 67 | SP | 3 | 3 | 22 | 13.2 |
| 40 | BRCA2 | c.5247T>G | Tyr1749Ter | 65 | EC ⁺ | 3 | 1c | 21 | 7.1 |
| 59 | BRCA1 | c.3756-59delGTCT | Ser1253fs | 54 | SP | 3 | 3b | 21 | 16.4 |
| 14 | BRCA1 | c.122A>G | His41Arg | 52 | SP | 3 | 3c | 26 | 2.1 |
| 191 | BRCA2 | c.6275_6276delTT | Leu2092fs | 68 | SP | 3 | 3c | 11 | 1.4 |
| 137 | BRCA2 | c.4154C>G | Ser1385Ter | 66 | SP | 3 | 4 | 11 | 0.7 |
| 90 | BRCA1 | c.1360_1361delAG | Ser 454Ter | 59 | SP | 3 | 1b | 26 | 60.2 |
| 168 | BRCA2 | Het del ex14-16 | | 52 | SP | 3 | 1c | 44 | 89.1 |
| 140 | BRCA1 | c.2641G>T | Glu881Ter | 49 | SP | 3 | 3c | 21 | 6.3 |
| 214 | BRCA1 | c.5153-26A>G | | 53 | SP | 3 | 3c | 13 | 5.5 |
| 232 | BRCA1 | c.4524G>A | Trp1508Ter | 45 | SP | 1 | 1c | 13 | 3.8 |
| VUS | | | | | | | | | |
| ID | Gene | DNA level | Protein level | Age | Cancer Pathology | Grade | Stage | MS | BOADICEA |
| 19 | BRCA2 | c.5278T>G | Ser1760Ala | 76 | SP | 3 | 3c | 14 | 4.4 |
| 31 | BRCA2 | c.4068G>A | Leu1356Leu | 70 | SP | 3 | 4 | 10 | 0.3 |
| 102 | BRCA2 | c.8072C>T | Ser2691Phe | 51 | SP | 3 | 3c | 15 | 1.8 |
| 101 | BRCA2 | c.8111C>T | Ser2704Phe | 67 | SP | 3 | 3c | 18 | 11.8 |
| 162 | BRCA2 | c.6403A>C | Asn2135His | 68 | SP | 3 | 3b | 10 | 0.9 |
| 215 | BRCA1 | c.1534C>T | Leu512Phe | 52 | EC | 1 | 1a | 13 | 6.8 |
| 54 | BRCA2 | c.1798T>C | Tyr600His | 72 | SP | 3 | 3c | 11 | 0.8 |
| | BRCA2 | c.1909+8_1909+9delTG at the exon10/intron10 boundary | | | | | | | |
| | BRCA2 | c.7504C>T | Arg2502Cys | | | | | | |
| 166 | BRCA2 | c.506A>G | Lys169Arg | 72 | SP | 3 | 1c | 10 | 0.5 |
| 176 | BRCA2 | c.1460C>A | Ala487Glu | 41 | SP | 3 | 3c | 21 | 28.4 |
| 111 | BRCA2 | c.8905G>A | Val2969Met | 83 | SP | 3 | 3c | 10 | 0.1 |
| 150 | BRCA1 | c.1534C>T | Leu512Phe | 72 | SP | 3 | 3c | 10 | 0.6 |
| 20 | BRCA2 | c.68-7T>A | | 74 | SP | 3 | 3c | 10 | 0.7 |
| 1 | BRCA1 | c.1563A>G | Ala521Ala | 55 | EC | 1 | 1a | 14 | 4.1 |
| 28 | BRCA2 | c.223G>C | Ala75Pro | 70 | EC | 3 | 1c | 30 | 4.4 |
| 223 | BRCA2 | c.967G>T | Val323Leu | 64 | EC | 2 | 1c | 10 | 2.5 |

Table S2. BRCA1/BRCA2 Mutations and VUS identified in the study

⁺ = High grade adenocarcinoma with features in favour of a grade 3 endometrioid adenocarcinoma

| | | Current patient testing pathway (£) | | | GTEOC patient testing pathway (£) | | |
|-----------------------|------|-------------------------------------|--------------------------------|-------------------------------|-----------------------------------|--------------------------------|-------------------------------|
| | | Budget | Average cost per BRCA positive | Average cost per test offered | Budget | Average cost per BRCA positive | Average cost per test offered |
| Base case, £850, 50% | | 142,702 | 11,892 | 2,265 | 253,617 | 14,919 | 1,093 |
| Cost of test | | | | | | | |
| | £650 | 130,102 | 10,842 | 2,065 | 207,217 | 12,189 | 893 |
| | £499 | 120,589 | 10,049 | 1,914 | 172,185 | 10,129 | 742 |
| | £350 | 111,202 | 9,267 | 1,765 | 137,617 | 8,095 | 593 |
| | £190 | 101,122 | 8,427 | 1,605 | 100,497 | 5,912 | 433 |
| Percentage referral | | | | | | | |
| | 0% | 105,772 | 8,814 | 1,679 | 253,617 | 14,919 | 1,093 |
| | 25% | 124,454 | 10,371 | 1,975 | 253,617 | 14,853 | 1,093 |
| | 75% | 160,950 | 13,412 | 2,554 | 253,617 | 14,853 | 1,093 |
| | 100% | 179,197 | 14,933 | 2,844 | 253,617 | 14,853 | 1,093 |
| GTEOC age cut-off <70 | | | | | | | |
| £850, 50% | | 142,702 | 11,892 | 2,265 | 148,429 | 9,895 | 1,091 |
| Scenario | | | | | | | |
| £650, 50%, <70 age | | 130,102 | 10,842 | 2,065 | 121,229 | 8,082 | 891 |

Table S3: Base case analysis results plus sensitivity analysis of patient testing pathway budget, average patient pathway cost of BRCA positive, and average patient pathway cost per genetic test offered for the 232 women eligible for the GTEOC study. In the GTEOC testing pathway all the patients were given the genetic test. The budget is the overall cost of all patients receiving eligibility checks, counselling and genetic testing plus post-test work-up i.e., the average cost per test offered is the total budget divided by the number of tests offered which is 232. For the current testing pathway, we calculated the Manchester score for all patients and based on this, 63 patients would have been eligible for genetic testing and offered the test. For these patients the full work-up cost was calculated from eligibility check to test and post-test work-up. For the base case we then assumed that 50% of the remaining 169 patients would have still been referred for genetic test counselling and so would incur those costs. We calculated for these 84 patients the cost of eligibility and genetic counselling but did not include test costs as these patients did not meet test criteria. For

the remaining 85 patients we only included the cost of checking eligibility for the referral. The sum of these three sets of costs for the 232 patients equal the budget and the average cost per test offered is that budget divided by the number of tests offered (i.e., total budget divided by 63).

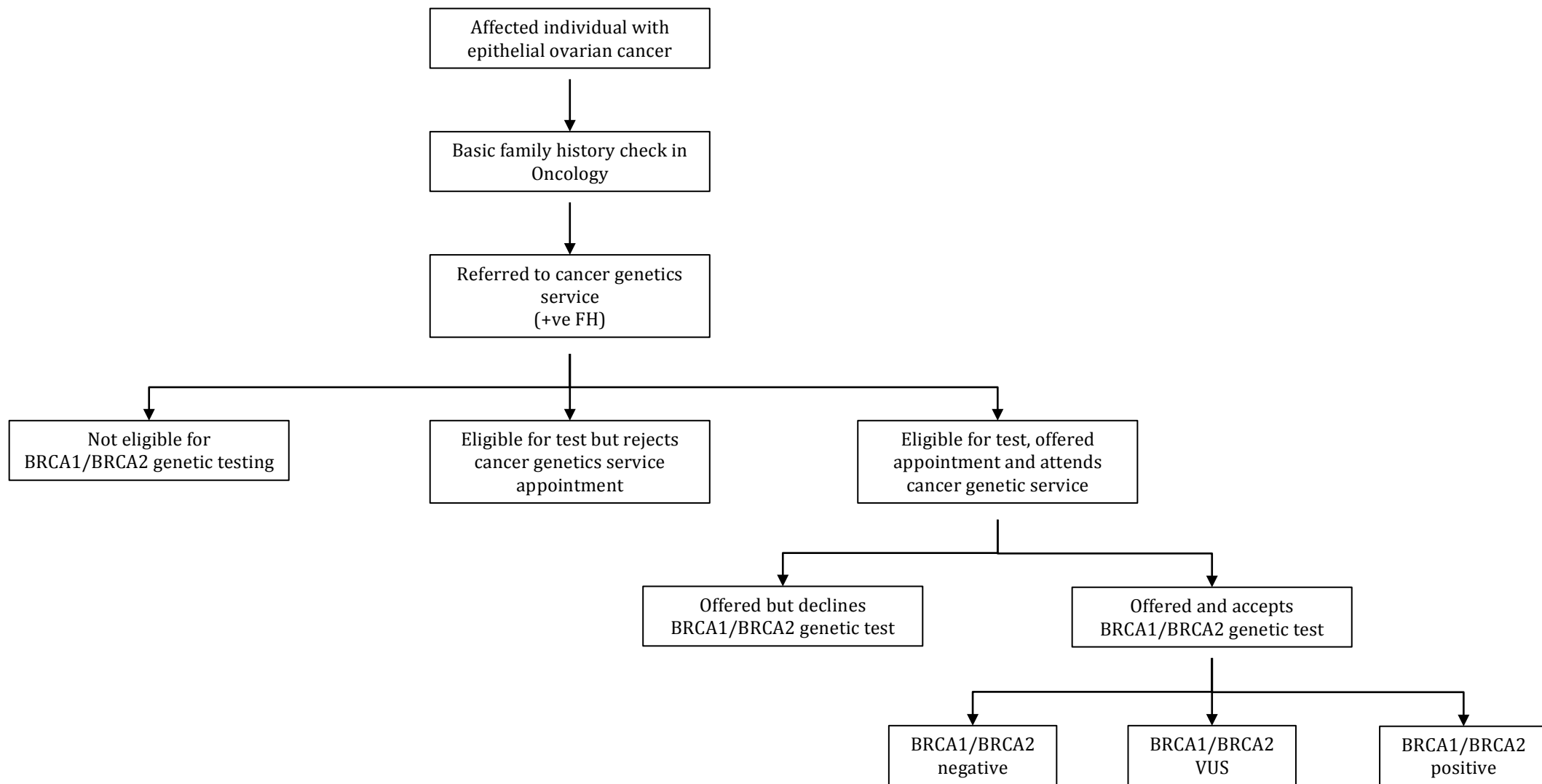


Figure S1: Patient pathway for the current provision of *BRCA1/BRCA2* testing in epithelial ovarian cancer patients

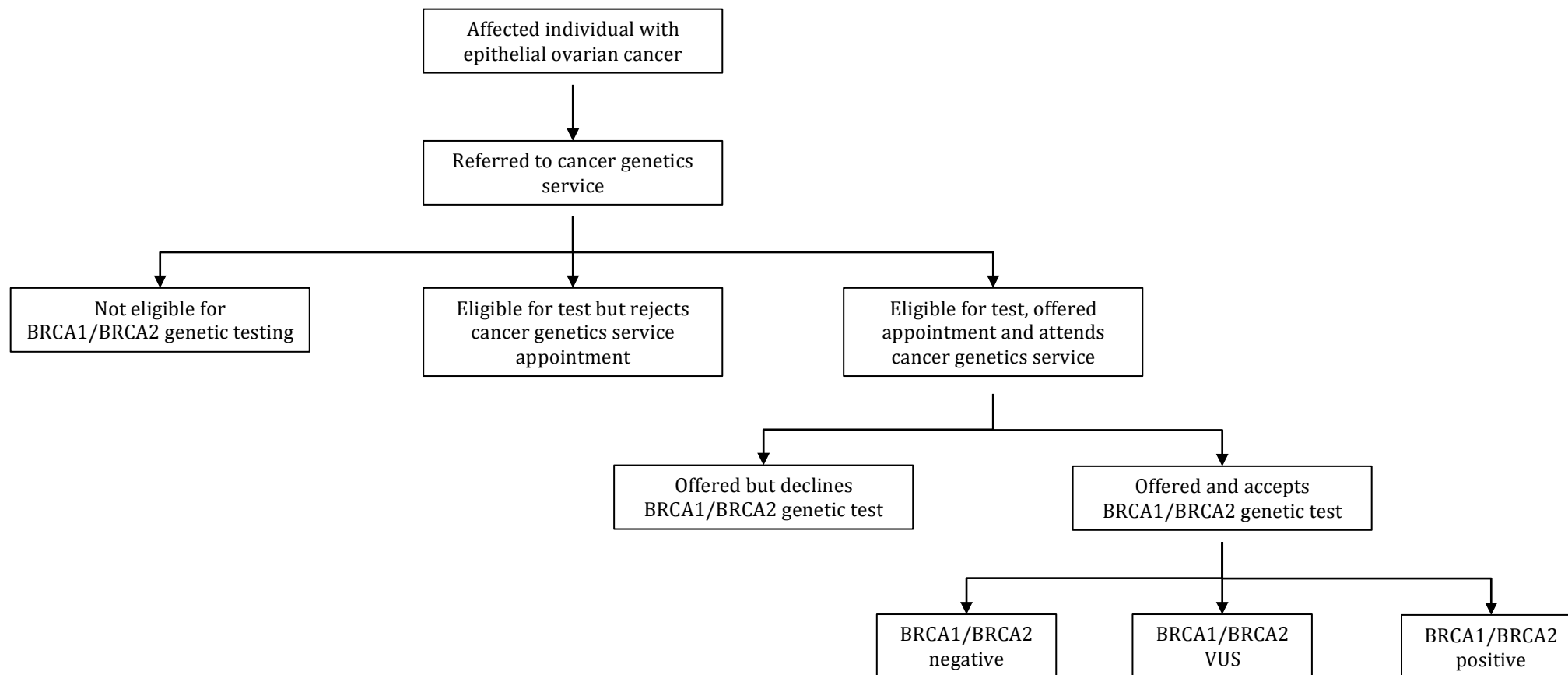


Figure S2: Proposed patient pathway for the provision of *BRCA1/BRCA2* testing in epithelial ovarian cancer patients from the GTEOC study.